Sodium-Calcium exchange, 2.4.3

- The sodium calcium exchanger is a membrane protein.
- It uses the energy stored in the sodium gradient to do work on calcium ions.
- Transports one calcium ion out of the cell (against the Calcium gradient).
- In exchange for letting three sodium ions in (along the Sodium gradient).
- It is electrogenic, i.e. each exchange changes the charge balance over the membrane.
- Net influx: $3 \times \text{Na}^+ - 1 \times \text{Ca}^{2+} = +e$

\[
\frac{dx_1}{dt} = k_{-1} n_i^3 x_2 + k_4 y_1 - (k_1 c_i + k_{-4}) x_1 \\
\frac{dx_2}{dt} = k_{-2} y_2 + k_1 c_i x_1 - (k_2 + k_{-1} n_i^3) x_2 \\
\frac{dy_1}{dt} = k_{-4} x_1 + k_3 n_e^3 y_2 - (k_4 + k_{-3} c_e) y_1 \\
1 = x_1 + x_2 + y_1 + y_2
\]

Flux in steady state:

\[
J = k_4 y_1 - k_{-4} x_1 = \frac{k_1 k_2 k_3 k_4 (c_i n_i^2 - K_1 K_2 K_3 c_e n_i^3)}{16 \text{ positive terms}}
\]

Sodium-Calcium exchange

An electrogenic exchanger

\[
\Delta G = G_{L_e} - G_{L_i} = (G_{L_e}^0 + RT \ln([L_e]) + zF V_e) - (G_{L_i}^0 + RT \ln([L_i]) + zF V_i) = RT \ln \left(\frac{[L_i]}{[L_e]}\right) - zF V
\]

Here we have used that $G_{L_e}^0 = G_{L_i}^0$ and $V = V_i - V_e$.

At equilibrium

\[
K = \frac{[L_i]_{eq}}{[L_e]_{eq}} = \exp \left(\frac{-zF V}{RT}\right)
\]
Back to the NCX case

\[ 3\text{Na}_3^+ + \text{Ca}_i^{2+} \rightarrow 3\text{Na}_i^+ + \text{Ca}_e^{2+} \]

Change in chemical potential:

\[ \Delta G = RT \ln \left( \frac{n_i^3 c_e}{n_e^3 c_i} \right) + FV \]

At equilibrium we have \( \Delta G = 0 \) thus:

\[ \frac{n_i^3 c_{eq}}{n_e^3 c_{eq}} = \exp \left( - \frac{FV}{RT} \right) \]

Detailed balance require that the product of the rates in each direction is equal:

\[ k_1 c_{i,eq} \cdot k_2 \cdot k_3 n_i^3 c_{eq} \cdot k_4 = k_{-1} n_i^3 c_{eq} \cdot k_{-4} \cdot k_{-3} c_{eq} c_{i,eq} \cdot k_{-2} \]

The membrane potential

Defining \( K_j = k_j/k_{-j} \) this becomes

\[ K_1 K_2 K_3 K_4 = \frac{c_{i,eq}}{c_{eq}} \frac{n_i^3}{n_i^3 c_{eq}} \]

Inserting into previous expression:

\[ K_1 K_2 K_3 K_4 = \exp \left( \frac{FV}{RT} \right) \]

The current expression then becomes:

\[ J = \frac{k_1 k_2 k_3 k_4 (c_i n_i^3 - c_{eq} n_i^3 e^F V / RT)}{16 \text{ positive terms}} \]

Flow through a semi-preamble membrane 2.6.1

Consider two solutions:
- A: Contains 100mM Cl\(^-\) ions and 100mM Na\(^+\) ions
- B: Contains 10mM Cl\(^-\) ions and 10mM Na\(^+\) ions

Both are neutral. If they are only separated by a membrane permeable to Cl\(^-\) but not Na\(^+\), this will happen:
- Cl\(^-\) will diffuse from A to B due the concentration gradient
- [Cl\(^-\)]\(_A\) will drop and [Cl\(^-\)]\(_B\) will increase
- [Na\(^+\)]\(_A\) and [Na\(^+\)]\(_B\) will remain fixed (no flow)
- A and B will no longer be neutral
- [Na\(^+\)]\(_A\) > [Cl\(^-\)]\(_A\) \( \Rightarrow \) \( A > 0 \), \( [\text{Cl}^-]_B > [\text{Na}^+]_B \) \( \Rightarrow \) \( B < 0 \).
- Cl\(^-\) will be attracted to A and repelled from B
The Nernst Equilibrium Potential

We now have two forces driving $\text{Cl}^-$ across the membrane:

- Flow from A to B due to the concentration gradient
- Flow from B to A due to the charge gradient

At some point an equilibrium is reached where the net flow is zero. The transmembrane potential at that point is called the Nernst Equilibrium Potential.

An expression for this potential will now be derived.

Plank’s equation, 2.6.3

Models the ion-flux caused by an electrical field:

$$ J = -u \frac{z}{|z|} c \nabla \phi $$

with

- $u$ - mobility of the ions in the liquid
- $z/|z|$ - sign of the charge of the ion
- $c$ - the concentration of the ion
- $\nabla \phi$ - the electrical field

The Nernst Equilibrium Potential, via Gibbs

Gibb’s free energy on either side of the membrane:

$$ G_{S,i} = G^0_S + RT \ln([S]_i) + zFV_i $$
$$ G_{S,e} = G^0_S + RT \ln([S]_e) + zFV_e $$

Electro-chemical potential difference:

$$ \Delta G_S = G_{S,i} - G_{S,e} = RT \ln([S]_i/[S]_e) + zFV $$

At equilibrium, $\Delta G_S = 0$:

$$ V_S = \frac{RT}{zF} \ln\left(\frac{[S]_e}{[S]_i}\right) $$

Fick’s law:

$$ J = -D \nabla c $$

Relationship between $m$ and $D$:

$$ u = D \frac{|z|F}{RT} $$

here $R$ is the gas constant and $F$ is Faraday’s constant.

Combined effect of concentration gradient and an electric field:

$$ J = -D(\nabla c + \frac{zF}{RT} c \nabla \phi) $$
Nernst Equilibrium Potential

Consider equilibrium in 1D flow:

\[
\begin{align*}
\frac{dc}{dx} + \frac{zF}{RT} \frac{d\phi}{dx} &= 0 \\
1 \frac{dc}{dx} + \frac{zF}{RT} \frac{d\phi}{dx} &= 0
\end{align*}
\]

Integrating from inside (x=0) to outside (x=L) yields:

\[
\ln\left(\frac{c(L)}{c(0)}\right) = -\frac{zF}{RT} (\phi(L) - \phi(0))
\]

We define the transmembrane potential to be \(v = \phi_i - \phi_e\). The value of the transmembrane potential at zero flux is then

\[
v_{eq} = \frac{RT}{zF} \ln\left(\frac{c_e}{c_i}\right)
\]  

Equation (3) is referred to as the Nernst Equilibrium Potential.

Nernst-Planck equation:

\[
J = -D(\nabla c + \frac{zF}{RT} c \nabla \phi)
\]

Consider 1D flow through a channel and assume \(\nabla \phi\) is constant in space and that \(c\) and \(\phi\) are in steady-state.

\[
\frac{d\phi}{dx} = \frac{\Delta \phi}{\Delta x} = \frac{\phi(L) - \phi(0)}{L - 0} = \frac{\phi_e - \phi_i}{L} = -\frac{v}{L}
\]

The equation is reduced to an ODE:

\[
J/D = -\frac{dc}{dx} + \frac{zF}{RT} c(-v/L) = -\frac{dc}{dx} + kc
\]

where \(k = \frac{zFv}{RTL}\)

Ionic currents

For passive ionic channels the flow through it must obey the equilibrium potential, i.e. be zero when \(v = v_{eq}\). A number of models exists, two common are:

Linear:

\[
I(v) = g(v - v_{eq})
\]

Here \(g\) is the conductance of the channel.

Goldman-Hodgkin-Katz:

\[
I(v) = g v c_i - c_e \frac{e^{-\frac{zFv}{RT}}}{1 - e^{-\frac{zFv}{RT}}}
\]

Derived from Nernst-Planck equation with assuming a constant (non-zero) field strength.

The equation

\[
J/D = -\frac{dc}{dx} + kc
\]

is solved by

\[
e^{-kx} c = c_i + \frac{J}{Dk} \left( e^{-kx} - 1 \right)
\]

We determine \(J\) by using \(c(L) = c_e\):

\[
J = Dk c_i - c_e \frac{e^{-kL}}{1 - e^{-kL}} = \frac{zFv c_i - c_e e^{-\frac{zFv}{RT}}}{RTL} \frac{e^{-\frac{zFv}{RT}}}{1 - e^{-\frac{zFv}{RT}}}
\]

\(J\) has dimension moles per area per time, an expression for current is given by

\[
I = zFJ = \frac{D z^2 F^2}{L RT} \frac{c_i - c_e e^{-\frac{zFv}{RT}}}{1 - e^{-\frac{zFv}{RT}}}
\]

This is the Goldman-Hodgkin-Katz current equation.
Accumulation around the membrane, 2.6.4

The membrane has properties similar to a capacitor

- Consists of two conducting medias (intra- and extra cellular space)
- These are separated by an insulating material (the membrane)

The potential over a capacitor is proportional to the separated charge ($Q$):

$$V = Q/C_m$$

The factor $C_m$ is called the capacitance of the capacitor.

The cell membrane modeled as a leaky capacitor

As any real capacitor the membrane conducts some current. The flux of ions ($I_{ion}$) will cause a change in $q$ and thus $V$.

Consider the change over a time interval $\Delta t$. It follows that

$$\frac{\Delta V}{\Delta t} = \frac{1}{C_m} \frac{\Delta Q}{\Delta t}$$

and in the limit we get:

$$\frac{dV}{dt} = \frac{1}{C_m} \frac{dQ}{dt}$$

The term $\frac{dq}{dt}$ is called the capacitive current and is denoted $I_c$.

Electrical circuit model of the cell membrane

The membrane behaves like resistor and capacitor in parallel:

$$I_t = I_{ion} + I_c$$

If the loop is closed then $I_t = 0$. In that case all the ions passing the membrane accumulate and change the membrane potential accordingly.

Channel gating
Channel gating, 3.5

The conductance of a channel varies with time and with transmembrane potential. Model for current per membrane area:

\[ I(V, t) = g(V, t) \phi(V) \]  

(4)

Current through a single open channel is \( \phi(V) \) and the amount of open channels per membrane area is \( g(V, t) \).

Multiple sub-units, 3.5.2

For some channels it is more appropriate to model the gate as a series of several sub-gates. Example with two gates:

\[ S_{00} \xrightarrow{\alpha} S_{10} \xleftarrow{\beta} \]
\[ S_{01} \xrightleftharpoons{\alpha, \beta} S_{11} \]

Using law of mass action we get a system of four equation. Will try to reduce this number to one!

Two State \( K^+ \)-channel, 3.5.1

Assumes that the channel can exist in two states, closed(C) and open(O):

\[ C \xleftrightarrow{\alpha(v)} O \]

Applying law of mass action:

\[ \frac{d[0]}{dt} = \alpha(C)C - \beta(O)O \]

Dividing by the total amount of channels ([C]+[O]) yields

\[ \frac{dg}{dt} = \alpha(1 - g) - \beta g \]

where \( g \) is the portion of open channel (\([O]/([C]+[O])\)).

Combine the states \( S_{01} \) and \( S_{10} \) into \( S_1 = S_{01} + S_{10} \):

\[ \frac{dS_0}{dt} = \alpha S_{00} + \beta S_{11} - (\alpha + \beta)S_{01} \]
\[ + \frac{dS_1}{dt} = \alpha S_{00} + \beta S_{11} - (\alpha + \beta)S_{10} \]

\[ = \frac{dS_1}{dt} = 2\alpha S_{00} + 2\beta S_{11} - (\alpha + \beta)S_1 \]

Define \( S_0 = S_{00} \) and \( S_2 = S_{11} \), we can then write:

\[ S_0 \xrightarrow{2\alpha} S_1 \xrightarrow{\alpha / 2\beta} S_2 \]
Only two independent variables since $S_0 + S_1 + S_2 = S_T$, constant. Define $x_i = S_i/S_T$. Claim:

$$x_2 = n^2, \text{ with } \frac{dn}{dt} = \alpha(1 - n) - \beta n$$

**Sodium, 3.5.3**

Behavior of the Sodium conductance can not be described by a chain of identical gates.

Two subunits of type $m$ and one of type $h$.

\[
\begin{array}{cccc}
S_{00} & \rightarrow & S_{10} & \rightarrow & S_{20} \\
\uparrow & \beta & \downarrow & 2\beta & \downarrow \\
\gamma & \uparrow & \delta & \downarrow & \delta \\
S_{01} & \rightarrow & S_{11} & \rightarrow & S_{21} \\
\end{array}
\]

Here $S_{ij}$ denotes $i$ open $m$ gates and $j$ open $h$ gates. Arguments similar to the one used above leads to these equations for $m$ and $h$:

\[
\frac{dm}{dt} = \alpha(1 - m) - \beta m, \quad \frac{dh}{dt} = \gamma(1 - h) - \delta h
\]

**Sodium, alternative formulation**

\[
\begin{align*}
\frac{dc}{dt} &= -(\alpha + \delta)c + \beta g \\
\frac{dg}{dt} &= \alpha c - (\beta + \gamma)g \\
i &= 1 - c - g
\end{align*}
\]